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HEROIN ABUSERS PERFORMANCE ON THE TOWER OF LONDON TEST RELATES TO THE BASELINE EEG ALPHA2 MEAN FREQUENCY SHIFTS

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Abstract

Planning function deficit is a most consistent finding in neuropsychological studies of heroin addicts. The performance on the Tower of London Test (TLT) correlated with the duration of daily heroin abuse (DDHA) in our previous study. Alpha2 mean frequency in anterior/central derivations was also predicted by DDHA in the same patient population. This retrospective study was undertaken in order to understand better the relationships between observed neurological deviations in heroin abusers. Thirty three heroin addicts and 12 healthy males were evaluated with 14 neuropsychological tests and resting eyes closed EEG. Multivariate tests showed that performance on the difficult (5 move) problems of TLT was strongly predicted by the EEG alpha2 mean frequency shifts, and these relationships were generally mediated by chronic heroin length. However, post-hoc analyses at separate leads demonstrated that the relationships between cognitive variables and alpha2 mean frequencies at left hemisphere were independent from chronic heroin effects, whereas elevation of alpha2 frequency in right hemisphere was strongly predicted by chronic heroin intake length. The patients with extremely high alpha2 mean frequency at left central region were especially prone to failure in TLT, that might be due to the inability of the hypothesized alpha2 generating network, which normally projecting to the central and temporal derivations bilaterally and to the right posterior temporal derivation, to function appropriately. Hence, it was concluded that planning dysfunction in heroin abusers is related to alpha2 mean frequency shifts predominantly at central regions.

Key words: cognitive functions, drug addiction, EEG, heroin, Tower of London Test

Abbreviations: Antisocial personality (ASP); Attention-deficit/hyperactivity disorder (ADHD); Duration of daily heroin abuse (DDHA); Electroencephalography (EEG); Evoked Related Potentials (ERP); Five move tasks (5M); Four move tasks (4M); Tower of London Test (TLT); Wechsler Adult Intelligence Scale (WAIS)

Introduction

Most neuropsychological and electroencephalographic (EEG) studies of drug abusers showed less profound brain dysfunction in chronic opiate addicts compared to alcoholics or chronic psychostimulant users (Hill and Mikhael, 1979; Costa and Bauer, 1997; Rogers et al., 1999; Arzumanov, 2001; Bauer, 2002). Indeed, opiate addicts who maintain medication free abstinence for several months often do not demonstrate global brain function deficits when neuropsychological or electroencephalographic measures are used (Bruhn and Maage, 1975; Shufman et al., 1996; Costa and Bauer, 1997; Bauer, 1998; Davis et al., 2002), nevertheless, two studies demonstrated persisting prefrontal dysfunction in heroin ex-addicts who had been completely withdrawn from the drugs for three and more months (Papageorgiou et al., 2001; Lee and Pau, 2002). Hence, the existing data evidence, that chronic heroin abusers are characterized by 'focal' prefrontal rather than diffuse brain dysfunction.

Neuropshychological deficits in heroin abusers

Deficits in planning functions were consistently reported in three studies of opiate addicts, in which neuropsychological tests with considerable loading on planning cognitive components were used (Ornstein et al., 2000; Briun et al., 2001; Lee and Pau, 2002). In the study of Ornstein et al. (2000) and in our previous study (Briun et al., 2001), heroin addicts were not able to solve problems of the Tower of London Test (TLT) effectively. Moreover, the performance on the TLT was the only neuropsychological parameter, which was predicted by the duration of daily heroin abuse (DDHA) without abstinence length effects in our patient population.

In addition to planning dysfunction, some other neuropsychological deficits in opiate abusers were also reported. Medicated heroin addicts usually demonstrate impairment on psychomotor speed and attention tests, which may be in part attributed to sedative medication effects (Darke et al., 2000; Specka et al., 2000; Briun et al., 2001; Davis et al., 2002; Mintzer and Stitzer, 2002). A proportion of opiate addicts exhibits broader cognitive impairment in comparison to other patients, and this fact is usually interpreted as a premorbid or concomitant brain damage in some heroin addicts (Hill and Mikhael, 1979; Briun et al., 2002; Davis et al., 2002).

EEG studies in heroin abusers

Spectral power and ERP amplitude variables in heroin addicts strongly relate to abstinence length (Shufman et al., 1996; Bauer, 2001; Polunina and Davydov, 2004) and seem to be a consequence of catecholamine imbalances due to acute opiate withdrawal effects (Devoto et al., 2002). Most studies showed considerable or even complete normalization of EEG spectral power or amplitude of ERP components in heroin ex-addicts who maintained abstinence for at least three months (Shufman et al., 1996; Costa and Bauer, 1997; Bauer, 2001; Papageorgiou et al., 2001; Bauer, 2002).

Mean or peak frequencies of spontaneous EEG in heroin abusers were reported only twice. Gritz et al. (1975) demonstrated significant slowing of alpha rhythm (O1 and O2 leads) peak frequency in 10 methadone patients and the same trend in 10 abstinent subjects. In our previous study (Polunina and Davydov, 2004), the increase in alpha2 (10-13 Hz) mean frequencies in anterior/central regions correlated with the duration of daily heroin abuse without abstinence length effects in the same patient population, where poor performance on the TLT was registered. Whereas, slowing of alpha1 (8-10 Hz) mean frequency was significantly related to the amount of heroin, taken by these patients daily before withdrawal. The prolongation of ERP components latencies in heroin addicts was also reported (Bauer, 1998; Arzumanov, 2001; Papageorgiou et al., 2001), and the delay in N75 latency significantly correlated with years of heroin use, but not with abstinence length in the study of Bauer (1998).

Thus, the existing data evidence that chronic heroin consumption may induce long-term changes in brain functioning, which were registered as the impairment in planning functions in neuropsychological studies, and as the alpha2 mean frequency shifts or prolongation of ERP components in EEG studies. We have undertaken this retrospective study in order to understand better the relationships between observed neurological deviations in heroin abusers, so we studied the relationships between performance on the TLT, alpha bands mean frequencies shifts and the duration of chronic heroin intake. It was predicted, that the alpha2 mean frequency elevations underlay the poor performance on the TLT in heroin abusers, and these relationships were mainly mediated by chronic heroin effects in this patient population. Nevertheless, the independent effects of alpha bands mean frequencies at separate leads on the performance on the TLT were also expected.

Methods

Groups studied

Thirty three heroin abusers (all males) were recruited from the Moscow Research Practical Center of Prevention of Drug Addiction. All the patients injected heroin intravenously (i.v.) daily for at least four months and were receiving in-patient treatment in the Drug and Alcohol Dependency Unit during the period of the evaluation. Twelve healthy male volunteers with no history of alcohol or drug abuse were chosen to match the drug abuse group as closely as possible for age and years of education. Written informed consent was obtained from patient and control subjects.

Clinical assessment and selection principles

Clinical evaluations were done to exclude subjects with lifetime history of a major medical disorder, head injury with loss of consciousness for more than 5 min., heroin overdoses with hospitalizations to intensive care unit for more than one day, seizures or other paroxysmal states, or a major psychiatric illness. HIV-serology was negative, and a standard CBC and serum transaminase levels were in normal range in all included patients. At the admission all patients signed the regimen consent that included twenty-four-hour stay at the unit and limitation of outside contacts. This allowed to prevent using illicit drugs during the inpatient treatment. However, patients received psychotropic medication treatment for decreasing cravings. The prescribed drugs and dosages varied in each case and included neuroleptics, antidepressants, benzodiazepines and/or carbamazepine.

Detailed drug histories were taken prior to evaluation. The duration of daily heroin abuse (DDHA) was defined as the sum of periods of regular (daily) heroin use. The average amount of heroin taken per day was counted through the week before complete withdrawal. Subjects characteristics in accordance with the duration of daily heroin abuse are summarized in Table 1.

Procedure

Neuropsychological testing was conducted in two to three sessions in heroin addicts and in one to two sessions in healthy controls. The testing was stopped when the examinee stated that he was tired. Then the testing was continued on the next working day. The EEG was recorded within one week from the start of the neuropsychological testing, usually on the last session day.

Neuropsychological testing

A neuropsychological test battery consisting of the Tower of London Test (Shallice, 1982), the Wisconsin Card Sorting Test (Milner, 1963), the Delayed Alternation Test (Freedman and Oscar-Berman, 1986) and the Russian version of Wechsler Adult Intelligence Scale (Filimonenko and Timofeev, 1995) was administered. All the tests were given manually by one of us (A.P.).

Tower of London Test. We obtained the description of the task directly from Shalice (1982). This test consisted of 12 look-ahead puzzles in which three differently colored rings had to be moved from a starting configuration on three sticks of unequal length to a target position in a minimum number of moves (Figure 1). Four problems were 2 or 3 moves deep, four were 4 moves deep and four were 5 moves deep. The number of problems solved at the first attempt in less than 60 seconds was scored. After incorrect response examinees continued performing the same task and were not stopped until having found the right solution. Two parameters were included into the analysis: 1) number of effectively performed 4 move problems – TLT 4M; 2) number of effective 5 move problems – TLT 5M.

Wisconsin Card Sorting Test, Delayed Alternation Test, Wechsler Adult Intelligence Scale (Russian version) were given in a standard manner. The following neuropsychological scores were included into the analysis: perseverative errors of WCST; incorrect responses in the Delayed Alternation Test; scaled scores of WAIS.

EEG recordings and analysis

Eyes closed resting EEG data were collected from the 19 monopolar electrode sites of the International 10/20 system (Fp1/Fp2, F3/F4, C3/C4, P3/P4, O1/O2, F7/F8, T3/T4, T5/T6, Fz, Cz, Pz), referred to linked earlobes. A differential eye channel was used for the detection of eye movements. EEG signal was amplified using EEG machine (Neurokartograph-4, MBN) with bandpass filter settings 0.5 and 100 Hz and a 50-Hz notch filter. All signals were digitized online at a sampling rate of 256 Hz and with a resolution of 12 bits. Electrode impedances were below 5 KΩ. Each recording comprised 7 min.

The resulting time series were inspected visually for body movements, eye blinks, eye movements, EMG, ECG, rheogram and loose electrodes artifacts. Intervals identified as disturbed by artifacts were excluded from the spectral analysis. Thus, 96±15 (range 76 - 132) sec artifact-free epochs were available per individual.

Finally, 4 sec with 50% overlap epochs were obtained from artifact-free EEG tracings and submitted to a Fast Fourier Transform. The data of monopolar recordings at Fp1/Fp2, F3/F4, C3/C4, P3/P4, F7/F8, T3/T4, T5/T6, O1/O2, Fz, Cz and Pz were included into the analysis. For each derivation absolute power and mean frequency (the frequency point below and above which powers of the band range were equal to each other) were computed for theta2 (6-8 Hz), the alpha total (8-13), alpha1 (8-10 Hz), alpha2 (10-13 Hz), and beta1 (13-20 Hz) frequency bands.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 11 for Windows on a PC computer. As TLT 5M and TLT 4M ranged from 0 to 4 correct problems, these variables were analyzed as between subject factors in analyses of variance (ANOVAs). Initially, repeated-measures multivariate ANOVAs (MANOVAs) with frontal/central/parietal orientation, temporal/midline orientation and hemisphere (left/right) as within-subject factors were conducted in regard to F3/F4, C3/C4, P3/P4, F7/F8, T3/T4, T5/T6 derivations. When the MANOVA demonstrated significance (at $p<.05$), age, education, performance on the Vocabulary (as a premorbid intelligence) or Digit Symbol (as a sedation measure) subtests, power of theta2, total alpha, alpha1, alpha2 or beta1 at appropriate leads, amount of heroin per day and duration of daily heroin abuse were entered one by one as a covariate into multivariate analyses of covariance (MANCOVAs). Later on, appropriate univariate ANOVAs (for all 19 leads) and multinomial logistic regression analysis were performed to determine relationships between performance on the TLT and alpha band variables at separate leads.

The relationships between alpha mean frequencies at different leads were studied with paired t-tests. Alpha mean frequencies were considered as ‘equal’ when t-tests showed $ps>0.20$.

As WAIS subtests, WCST, Delayed Alternation Test and alpha mean frequencies met parametric test assumptions, interrelationships between these variables were analyzed by Pearson correlations.

Results

Multivariate and post-hoc tests of the relationships between the performance on the Tower of London Test and alpha bands variables

At least 10 subjects constituted each subgroup in accordance to the performance on the TLT 5M or TLT 4M. Thus, the TLT 5M subgroups included: 1) ten patients with TLT 5M = 1; 2) fifteen patients and 4 healthy controls with TLT5M = 2; 3) eight patients and 8 healthy controls with TLT 5M = 3 or 4. The TLT 4M subgroups included: 1) seventeen patients and 4 healthy controls with TLT 4M = 0-2; 2) nine patients and 3 healthy controls with TLT 4M = 3; 3) seven patients and 5 healthy controls with TLT 4M = 4.

Several main and interactive effects of derivation orientation factors on alpha bands variables were determined (Wilks' λs = .167 - .757, Fs(2,41) = 97.25 - 6.27, ps = .000-.004). Frontal/central/parietal orientation significantly affected both alpha bands power and mean frequency variables. Across the groups, alpha1 and alpha2 power was lower at central leads and higher at posterior leads. The alpha1 mean frequency was slower at central leads in comparison to frontal and parietal derivations, and oppositely the alpha2 mean frequency was the highest in central derivations compared to anterior and posterior ones in three groups. The described gradients were more pronounced in left hemisphere for alpha1 power (significant hemisphere factor interactive effect), and at midline leads for alpha1 and alpha2 mean frequencies (significant temporal/midline orientation interactive effect).

The significant interactive TLT group effects on alpha bands variables were detected only in the analyses of the relationships between the performance on the 5 move problems of TLT and alpha bands mean frequencies.

The TLT grouping factor significantly interacted with frontal/central/parietal and temporal/midline orientation factors along with hemisphere factor of alpha1 mean frequency distribution (Wilks' λ = .760, F(4,82) = 2.95, p =.025). Post-hoc univariate ANOVAs at separate leads demonstrated, that alpha1 mean frequency at T4 was significantly slower in the group with abnormal performance on the TLT 5M (1 completed task) in comparison to the group with good performance on the TLT 5M (3 or 4 completed tasks) (8.72±0.13 vs 8.92±0.17, F(2,42) = 4.72, p =.014, after Bonferroni correction p=.014). Entering the covariates, including theta2, alpha1 and alpha2 power at T4, did not influence the above relationships (ps remained at < 0.05).

Groups according to the performance on the 5 move problems of TLT significantly interacted with temporal/midline orientation along with hemisphere factor of alpha2 mean frequency distribution (Wilks' $\lambda = .835$, $F(2,42) = 4.06$, $p = .025$). This interactive group effect remained significant when each covariate except the duration of daily heroin abuse or amount of the drug per day was entered into the model. After the DDHA or the amount of heroin was entered only the trend for the above described interactive group effect was observed (ps=.080 and .061, respectively). Moreover, the duration of daily heroin abuse significantly interacted with alpha2 mean frequencies distribution in temporal/midline plane (Wilks' $\lambda = .887$, $F(1,41) = 5.08$, $p = .030$).

Post-hoc univariate ANOVAs demonstrated significantly higher alpha2 mean frequencies in group with TLT 5M=1 in comparison to subjects with TLT 5M≥3 at Fp2, F3, C3, T3, Cz, C4, T4 and T6 (Fs(2,42)=3.45-5.72, ps=.041-.006, after Bonferroni corrections ps=.007 - .044; see Fig. 2). Moreover, alpha2 mean frequencies of the group with TLT 5M=1 were significantly higher at C3 and Cz in comparison to subjects who performed two of TLT 5M problems (after Bonferroni corrections ps<.05). When the duration of daily heroin abuse was entered into the model as a covariate, the main effect of the TLT 5M was still significant only at C3 and Cz (ps=.031 and .051, respectively); whereas, the duration of daily heroin abuse significantly related to alpha2 mean frequencies at C4 and Cz (ps=.041 and .048, respectively). Thus, in the latter model the alpha2 mean frequency at C3 was independently predicted by the performance on the TLT 5M, the same variable at Cz was independently predicted by both the TLT 5M and the duration of daily heroin abuse, and alpha2 mean frequency at C4 was independently predicted only by the heroin abuse length.

When alpha2 mean frequencies at C3 and C4, alpha1 mean frequency at T4 and the duration of daily heroin abuse were entered into the post-hoc multinomial regression model as independent covariates, only alpha2 mean frequency at C3 significantly predicted the performance on the 5 move problems of TLT (final Cox and Snell's $R^2 = .43$, $\chi^2 = 25.27$, $df = 8$, $p = .001$; Likelihood Ratio Test $\chi^2 = 7.99$, $df = 2$, $p = .018$) along with statistical trend for alpha1 mean frequency at T4 and the duration of daily heroin abuse (Likelihood Ratio Tests $\chi^2 = 5.48$ and 4.89, $df = 2$, ps= .065 and .087, respectively).

Hence, the results of multivariate and post-hoc tests gave grounds to suggest that at least two sources of planning dysfunction existed in the studied population. The chronic heroin abuse significantly influenced the distribution of alpha2 mean frequencies at temporal/midline plane and strongly mediated the relationships between poor performance on the most difficult (5 move) tasks of TLT and the elevated alpha2 mean frequency at right central derivation. The high alpha2 mean frequency at C3 was the strongest predictor for the poor performance on the 5 move problems of TLT, and this effect seemed to be highly localized and independent from chronic heroin influences. In order to understand these findings better, we further explored the relationships between alpha2 mean frequencies at central leads and this EEG variable at other leads in regard to grouping factor, which integrated both the cognitive performance, and the addiction variables.

Relationships between alpha2 mean frequency at central leads and alpha2 mean frequencies in other derivations in healthy subjects and patient subgroups

Distribution of alpha2 mean frequencies were studied in four subject groups: (1) healthy subjects (each subject performed at least 2 tasks of TLT 5M); (2) heroin addicts who performed only one task of TLT 5M (abnormal performers, n=10); (3) heroin addicts of DDHA<1.5 years who performed at least 2 effective solutions; and (4) heroin addicts of DDHA>1.5 years who also performed at least 2 tasks of TLT 5M; however, the average performance of the latter group was significantly worse compared to the healthy group ($U=32$, $p=.018$; $n=11$). Figure 3, Tables 2 and 3 demonstrate, that alpha2 mean frequencies distributed differently in the studied groups.

In healthy controls, the alpha2 mean frequency at C3 was significantly higher compared to alpha2 mean frequencies in most other derivations including the nearest ones - Cz, F3 and P3; nevertheless, it was equal to this EEG parameter at more distant leads – T4 and T6 (Table 2). Alpha2 mean frequency at C4 in this group was somewhat lower compared to C3 (Table 3), and was equal to alpha2 mean frequencies in all temporal and central derivations; nevertheless, it was significantly higher compared to the nearest anterior derivation – F4. Thus, alpha2 mean frequencies at C3 and C4 were well balanced in healthy subjects, and were equal to alpha2 mean frequencies at T3, T4 and T6; the relationships of alpha2 mean frequency at C4

seemed to be somewhat more 'diffuse' and included also Cz, F7, F8 and T5 in this group.

In heroin addicts with abnormal performance on the TLT 5M, alpha2 mean frequencies were abnormally high in all derivations, and this EEG parameter was extremely elevated at C3. Alpha2 mean frequency at C3 was equal only to this variable at Cz in this patient subgroup. As in healthy controls, alpha2 mean frequency at C4 was equal to this variable at all right lateral, T3 and Cz derivations. In contrast to healthy group, alpha2 mean frequency at C4 in these patients was also equal to this variable at F3, Fz and F4.

In heroin addicts of DDHA<1.5 years with performance on the TLT 5M in normal range, alpha2 mean frequency at C3 was equal to almost all derivations except C4. As in healthy controls, alpha2 mean frequency at C4 was equal to this variable at Cz, T3, T4 and T5; and, in contrast to healthy group, alpha2 mean frequency at C4 was significantly higher in comparison to this variable at C3, F7 and T6 in these patients.

In heroin addicts of DDHA>1.5 years who performed at least two tasks, the alpha2 mean frequencies were abnormally high in all derivations, and this EEG variable was extremely elevated at C4. Alpha2 mean frequency at C3 was also elevated but to a lesser degree and was equal to this variable at most other derivations. It is important, that alpha2 mean frequency at C3 was not equal to this variable at T6 in the group of DDHA>1.5 years.

Hence, the distribution of alpha2 mean frequencies in four studied groups evidenced that at least two alpha2 generating systems projected to central derivations and probably played somewhat different role in the performance on the TLT. In *healthy individuals*, these two alpha2 generating systems oscillated at well balanced frequencies, nevertheless, they still might be recognized. The alpha2 system, that projected mostly to C3 (C3-alpha2), displayed stronger relationships with distant right temporal derivations compared to the nearest ones in left hemisphere (except T3). At the same time, alpha2 system, that projected to C4 (C4-alpha2), was characterized by bilateral relationships with temporal derivations in healthy group. In heroin addicts with *abnormal performance* on TLT 5M, the C3-alpha2 seemed to be severely disintegrated and oscillated at the alpha2 frequency, that could not be accepted by other brain regions; C4-alpha2 was also imbalanced in these patients. In *heroin addicts of DDHA<1.5 years* with the performance on the TLT in normal range, two

'central' alpha2 generating systems oscillated at poorly balanced frequencies probably due to the abnormal elevation of frequency in C4-alpha2. Nevertheless, the temporal derivations seemed to be still 'under the control' of both alpha2 systems in these patients. In *heroin addicts of DDHA>1.5 years*, who performed at least 2 problems of TLT 5M, the C4-alpha2 seemed to be severely disintegrated. Moreover, the C3-alpha2 appeared to be secondarily affected by the changes in the former one.

Correlations between alpha2 mean frequencies and neuropsychological tests

Alpha2 mean frequencies significantly correlated at $p \leq 0.01$ level with the performance on the Comprehension (the maximal r=-.511 at P3) and Block Design (the maximal r=-.424 at F3) in all studied derivations, and with the Object Assembly at T3 and T4 (maximal r=-.403 at T3). After entering the duration of chronic heroin as a covariate all the above correlations remained significant at $p<0.05$ level. No significant correlations between alpha2 mean frequencies and other eight subtests of WAIS, the performance on WCST or Delayed Alternation Test were determined.

Discussion

As it was predicted, the relationships between performance on the most difficult (5 move) problems of TLT and alpha2 oscillations were mediated by the duration of daily heroin abuse in the studied population. However, the chronic heroin effects on brain functions appeared to be stronger at right hemisphere compared to the left one, and were negligible at the left central derivation. The distribution of alpha2 mean frequencies at central temporal/midline plane demonstrated different patterns in subgroups of healthy and patient subjects. The latter findings might be interpreted as the evidence of the existence of at least two alpha2 generating systems, that projected to left and right central derivations and displayed diverse functioning patterns in healthy subjects and patient subgroups. Moreover, three other cognitive variables (Comprehension, Block Design and Object Assembly subtests of WAIS) strongly correlated with alpha2 mean frequencies independently from the chronic heroin effects, and these correlations were most pronounced at left hemisphere.

Neural correlates of the Tower of London Test

Effective solutions of the difficult tasks of the TLT require simultaneous integration of the considerable amount of sequential and spatial information, which must be

performed at the first attempt and within a short period of time. These requirements are unique characteristics of the TLT in comparison to the other used in this study neuropsychological tests.

Neuroimaging studies in healthy subjects demonstrated wide-spread bilateral activation of the brain while performing the TLT (Andreasen et al., 1992; Baker et al., 1996; Owen et al., 1996; Newman et al., 2003), and this multiple region brain activation was especially pronounced while solving difficult problems of the test (Baker et al., 1996; Newman et al., 2003). Insignificance of baseline EEG power asymmetries for the performance on the TLT was shown in the study of Hoptman and Davidson (1998). The latter findings contrasted to the strong correlations between baseline EEG asymmetries patterns and performance on the Verbal Fluency and Corsi's Recurring Blocks tests in the cited study. Thus, in normal subjects balanced activity of both hemispheres appear to play an important role while performing TLT.

Shallice (1982) reported pronounced deficit in the TLT in neurological patients with the lesions in anterior regions of the left hemisphere. In the same study, patients with lesions in right anterior, left posterior or right posterior regions performed the test at the level of healthy controls. Andreasen et al. (1992) found lack of the appropriate activation of the left mesial frontal cortex in schizophrenic patients who performed TLT significantly worse compared to healthy subjects. Elliott et al. (1997) demonstrated significantly lower activation of the left anterior cingulate, left caudate and right prefrontal cortex in depressed patients in comparison to healthy controls while performing difficult problems of TLT. As may be expected, the latter patient group showed poor performance on the test. Thus, the studies of pathological populations evidenced that the failure in planning functions might be related at least in part to local activation deficits at the left anterior medial region of the brain in these patients. The evidence of the existence of a left medial centre, which might play a principle role while performing difficult problems of TLT was also demonstrated in healthy subjects in the neuroimaging study of Owen et al. (1996).

In our study the patients who performed only one from four tasks of TLT 5M demonstrated extremely abnormal alpha2 oscillations at C3 during resting EEG, and these oscillations did not seem to 'recruit' appropriate brain regions. At the same time, patients with abnormally high alpha2 mean frequency at C4 also demonstrated significantly worse results on the 5 move tasks compared to healthy controls, however, they performed TLT still significantly better compared to 'abnormal' group.

Thus, the C3-alpha2 seemed to play a critical role in the TLT performance, whereas C4-alpha2 appeared to realize 'supportive' functions in the recruitment of right hemisphere networks.

Von Stein and Sarnthein (2000) demonstrated the inverse relationship between the 'globality' of cognitive processes and frequency of interactions between neuronal networks. The authors showed, that local interactions (during visual processing) involve gamma frequency dynamics, semantic interactions between temporal and parietal cortex involve beta1 frequency dynamics, and long-range interactions (working-memory-retention, etc.) involve interactions in low (theta and alpha) frequency range.

In the context of the hypothesis of Von Stein and Sarnthein, it becomes clear why the increase of alpha2 frequencies negatively affected some (but not all) cognitive functions in our patients. The dysfunctional C3-alpha2 recruiting center in 'abnormal' group was not able to connect to other members of appropriate neuronal network at such an extremely high frequency. The abnormal C4-alpha2 in heroin addicts with long heroin abusing history was not able to interact with other brain areas effectively either. Nevertheless, being supportive in the context of the TLT, the C4-alpha2 affected planning functions to a lesser degree. In heroin addicts with relatively short heroin abusing history, alpha2 frequencies were also elevated, but as it may be seen from the paired t-tests analyses and behavioral performance (TLT), central alpha2 centers were still able to integrate appropriate neuronal networks in this patient subgroup.

Lateralized brain dysfunction in populations at high risk for drug abuse

Drug abusers constitute a heterogeneous population, that includes various subgroups with diverse psychiatric comorbidities, and the latter may contribute to cognitive impairment in these patients (Ling et al., 1996). Strong associations between cognitive functions and alpha2 frequencies in left hemisphere, that were not removed by the chronic heroin factor, give grounds to suggest premorbid left hemisphere dysfunction in a subgroup of studied heroin abusers (which, nevertheless, might be worsened due to the chronic heroin effects). Some literature data are in agreement with the latter hypothesis.

Barry et al. (2002) reported higher coherences in left hemisphere compared to the right one in normal children. In children with attention-deficit/hyperactivity

disorder (ADHD) the laterality effect was reduced in alpha bands. Moreover, in ADHD group the long-range intrahemispheric and interhemispheric coherences in alpha (7.5-12.5 Hz) band were decreased. Thus, the maturational lag in the development of alpha networks in this population at risk for drug abuse might adversely affect the functions of left hemisphere as an "organizing" center of the brain. Indeed, our patients with abnormally increased alpha2 frequencies in left hemisphere demonstrated extremely poor performance on the Comprehension test – the verbal measure of 'common sense', and this fact might reflect the developmental deviation of verbal cognition in this patient subgroup. Deficits in verbal abstraction were reported in another population of high risk for drug abuse – individuals with antisocial personality disorder (Stevens et al., 2003).

Deckel et al. (1996) reported alpha2 power asymmetry in F3/F4 to be predictive of the antisocial personality diagnosis (ASP) and childhood problem behaviors in non-drug abusing males. Interestingly, that authors measured alpha2 as activity of 10.9-12.4 Hz, that constituted a higher boundary between 'healthy' and 'increased' alpha2 mean frequencies in our study. Hence, the cited data may be interpreted as an excess of 'abnormal' alpha2 oscillations in left hemisphere in this group. Moreover, planning deficit (Porteuz Maze test) was also predictive of ASP and Conduct disorders in this study, but did not correlate with fast alpha measures. The latter finding is consistent with our data about poor predictive value of resting alpha power measures toward cognitive variables.

Thus, heroin addicts with 'abnormal' performance on the TLT and extremely high alpha2 mean frequency in left central derivation seemed to represent a subgroup with premorbid left hemisphere dysfunction.

Lateralized brain dysfunction in chronic heroin abusers

Stronger relationships between alpha2 mean frequencies in the right hemisphere and the duration of daily heroin abuse give grounds to suggest the higher sensitivity of right hemisphere to adverse chronic heroin effects in comparison to the left brain. Indeed, we have not found any study that demonstrated predominantly left hemisphere impairment in heroin abusers, whereas at least two electrophysiological studies showed severer right brain dysfunction in heroin abusers as a whole population.

Two research groups reported prolongation of latencies of cognitive ERP predominantly in the right hemisphere in heroin addicts (Arzumanov, 2001; Papageorgiou et al., 2001). In the study of Papageorgiou et al. (2001) latency of component P600 was significantly prolonged only in right derivations, most prominently at Fp2 and at the half way between C4/T6. The latter finding was observed in heroin ex-addicts who maintained complete abstinence for at least 6 months.

Speculatively, the specificity of the information processing modes may make the right hemisphere to be especially prone to chronic heroin effects. Two experimental studies demonstrated opioids' ability to remodel the density of dendritic spines and thus to affect the synaptic inputs and probably neuronal oscillation frequencies (Morozov and Bogolepov, 1984; Robinson et al., 2002). Hypothetically, the synaptic modulation may adversely affect the right hemisphere functions inproportionally greater in comparison to the left one.

Strengths and limitations of the study

The present data were obtained at the final of 'heroin epidemics' in Russia (1999-2000), during which many drug-naïve, healthy and intelligent young people were exposed and addicted to heroin as easily available and the cheapest substance at criminal market. Relatively short duration of heroin intake along with young age minimized the contribution of concomitant diffuse brain injury factors in the studied population. Small doses of heroin in our patients evidenced low contamination of the drug at that period. Nevertheless, patients in this study received psychotropic medication, which varied in each case and could not be included into the analyses directly. Another limitation of the present study concerns the lack of the sophisticated evaluation of concomitant psychiatric disorders in the studied population. Thus, further studies in drug free or methadone maintained patients are needed in order to confirm the present preliminary findings and to assess the effects of the concomitant psychiatric disorders on the relationships between alpha2 mean frequencies distribution and cognitive functions in heroin addicts.

Conclusion

Heroin abusers performance on the difficult (5 move) problems of Tower of London Test is strongly predicted by the EEG alpha2 mean frequency shifts, and these

relationships are generally mediated by chronic heroin length in this patient population. The chronic heroin effects on brain functioning are especially pronounced at right hemisphere, whereas the relationships between cognitive functions and alpha2 mean frequency shifts in left hemisphere might reflect at least partially a premorbid left brain dysfunction in a proportion of heroin addicts. Extremely high alpha2 frequency at the left central region appears to underlie the poor performance on the TLT due to the inability of the alpha2 generating network, which normally projecting to the central and temporal derivations bilaterally and to the right posterior temporal derivation, to function appropriately. High alpha2 mean frequency at right central region might affect the performance on the difficult problems of TLT secondarily by disturbing the alpha2 oscillations spread from the central left derivation to the right posterior temporal regions.

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Table 1. Subject Characteristics

	DDHA<1.5 subjects	DDHA>1.5 subjects	Control subjects	Test	Bonferroni or Mann-Whitney post-hoc result
N	17	16	12		
Age	21.7±3.1	24.6±5.3	24.8±4.1	F =3.5*	C>(DDHA<1.5)
Years of education	13.1±1.9	12.7±2.7	13.8±2.2	F =1.4	NS
Vocabulary (WAIS)	12.8±2.7	13.3±2.5	14.3±2.1	F =1.3	NS
Digit Symbol (WAIS)	6.6±1.4	7.1±1.7	10.5±2.9	F =15.0**	C>(DDHA<1.5), C>(DDHA>1.5)
TLT total	8.59±1.84	7.81±1.33	9.33±1.56	χ^2 = 4.8	NS
TLT 4M	2.82±1.07	2.19±0.98	3.00±1.03	χ^2 = 4.5	NS
TLT 5M	2.18±1.01	1.81±0.66	2.83±0.73	χ^2 = 9.2**	C>(DDHA>1.5)
Alpha2 mean frequency					
C3	11.09±0.30	11.21±0.33	10.92±0.25	F = 3.6*	C<(DDHA>1.5)
Cz	11.10±0.31	11.21±0.32	10.85±0.25	F = 5.5**	C<(DDHA>1.5)
C4	11.13±0.28	11.23±0.32	10.86±0.23	F = 6.3**	C<(DDHA<1.5), C< (DDHA>1.5)
Years of daily heroin use	0.73±0.29	2.35±0.59	-	t =-10.4**	(DDHA>1.5)>(DDHA<1.5)
Grams of heroin per day	0.42±0.34	0.43±0.26	-	t = -.154	NS
Days of abstinence	13 (6-60)	12 (8-141)	-	U = 132.5	NS

All values are expressed as mean ± SD.

Abbreviations: F, ANOVA F; χ^2, Kruskal Wallis test; t, independent samples t-test; U, Mann-Whitney test; DDHA<1.5, duration of daily heroin abuse less than 18 months; DDHA>1.5, duration of daily heroin abuse more than 18 months; C – controls; WAIS, Wechsler Adult Intelligence Scale; TLT, Tower of London Test; 4M or 5M, four or five move problems of the TLT; NS – not significant.

* $p<0.05$; ** $p<0.01$

Table 2. Relationships between the alpha2 mean frequency at C3 and alpha2 mean frequencies in other derivations in four subject subgroups

	Healthy controls n=12	Heroin addicts with TLT 5M=1 DDHA=0.5-3.7 n=10	Heroin addicts with TLT 5M>1 and DDHA<1.5 n=12	Heroin addicts with TLT 5M>1 and DDHA>1.5 n=11
Fp1	T=2.70, p=.019	T=2.94, p=.016	**T=0.20, p=.845**	**T=1.15, p=.275**
Fp2	T=2.77, p=.017	T=2.67, p=.026	**T=0.34, p=.740**	**T=0.64, p=.536**
F3	T=3.12, p=.009	T=1.88, p=.093	**T=0.27, p=.795**	T=1.82, p=.096
Fz	T=3.41, p=.005	T=2.00, p=.077	**T=-0.41, p=.689**	T=1.75, p=.108
F4	T=3.68, p=.003	T=2.20, p=.055	**T=-0.56, p=.586**	**T=0.74, p=.474**
F7	T=1.48, p=.165	T=2.95, p=.016	**T=0.94, p=.368**	T=1.91, p=.082
F8	T=2.21, p=.047	T=2.10, p=.066	**T=0.00, p=1.00**	**T=0.82, p=.429**
Cz	T=2.92, p=.013	**T=1.00, p=.343**	**T=-1.10, p=.295**	**T=0.62, p=.551**
C4	**T=1.29, p=.222**	T=1.62, p=.140	T=-2.28, p=.043	**T=-1.16, p=.269**
T3	**T=0.38, p=.711**	T=2.86, p=.019	T=-1.74, p=.111	**T=0.94, p=.368**
T4	**T=0.92, p=.374**	T=2.38, p=.041	**T=-1.17, p=.266**	**T=-0.77, p=.457**
T5	T=2.01, p=.068	T=3.29, p=.009	**T=-1.07, p=.306**	**T=1.12, p=.286**
T6	**T=1.11, p=.291**	T=4.00, p=.003	**T=-0.43, p=.674**	T=2.17, p=.055
P3	T=3.66, p=.003	T=2.97, p=.016	**T=-0.16, p=.878**	**T=0.73, p=.480**
Pz	T=1.94, p=.076	T=2.30, p=.047	**T=1.11, p=.293**	T=2.45, p=.032
P4	T=2.52, p=.027	T=2.23, p=.052	**T=0.56, p=.586**	T=3.22, p=.008
O1	T=3.34, p=.006	T=3.07, p=.013	**T=1.33, p=.217**	T=1.74, p=.109
O2	T=2.97, p=.012	T=2.29, p=.048	T=1.48, p=.166	T=3.96, p=.002

All values are expressed as Student's T and its respective *p* value. Non-significant paired t-tests with ps>0.2 are printed in bold typeface.

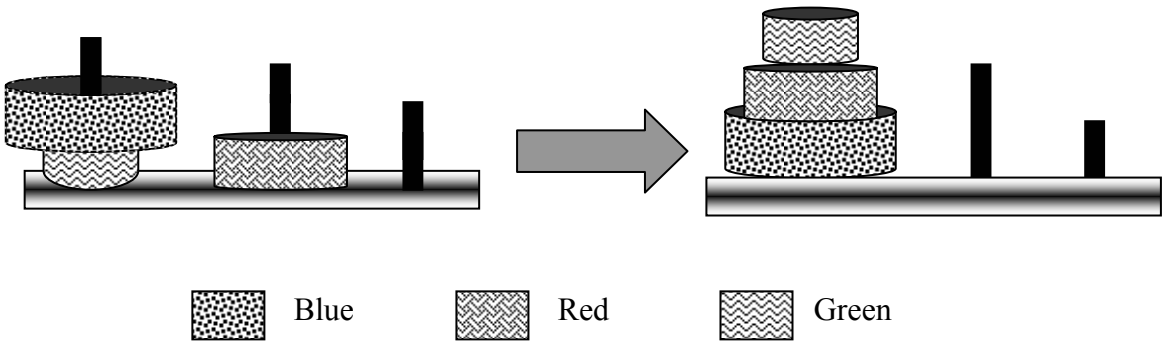
Abbreviations: see Table 1.

Table 3. Relationships between alpha2 mean frequency at C4 and alpha2 mean frequencies in other derivations in four subject subgroups

	Healthy controls n=12	Heroin addicts with TLT 5M=1 DDHA=0.5-3.7 n=10	Heroin addicts with TLT 5M>1 and DDHA<1.5 n=12	Heroin addicts with TLT 5M>1 and DDHA>1.5 n=11
Fp1	T=1.81, p=.095	T=1.77, p=.111	T=2.06, p=.064	T=1.84, p=.096
Fp2	T=1.95, p=.075	T=1.41, p=.193	T=1.96, p=.076	T=1.55, p=.151
F3	T=1.74, p=.108	**T=0.83, p=.427**	T=2.28, p=.044	T=3.75, p=.004
Fz	T=2.11, p=.056	**T=1.05, p=.322**	**T=1.25, p=.239**	T=2.97, p=.014
F4	T=2.66, p=.021	**T=1.21, p=.259**	**T=1.25, p=.239**	T=2.32, p=.042
F7	**T=0.45, p=.650**	T=1.96, p=.081	T=2.49, p=.030	T=3.83, p=.003
F8	**T=1.24, p=.237**	**T=0.85, p=.415**	T=2.02, p=.069	T=2.67, p=.024
Cz	**T=0.49, p=.636**	**T=-0.61, p=.560**	**T=1.00, p=.339**	T=2.06, p=.067
C3	**T=-1.29, p=.222**	T=1.62, p=.140	T=2.28, p=.043	**T=1.16, p=.269**
T3	**T=-0.75, p=.468**	**T=0.76, p=.468**	**T=0.62, p=.551**	T=2.17, p=.055
T4	**T=-0.62, p=.549**	**T=0.76, p=.468**	**T=0.23, p=.820**	**T=0.32, p=.756**
T5	**T=0.69, p=.502**	T=2.01, p=.075	**T=0.43, p=.674**	T=2.45, p=.034
T6	**T=-0.15, p=.886**	**T=0.69, p=.509**	T=2.60, p=.025	T=3.34, p=.009
P3	T=3.42, p=.005	T=1.86, p=.096	T=1.54, p=.151	T=1.99, p=.074
Pz	T=1.41, p=.183	T=1.50, p=.168	T=2.45, p=.032	T=3.53, p=.005
P4	T=1.44, p=.175	T=1.49, p=.170	T=2.42, p=.034	T=3.99, p=.003
O1	T=2.99, p=.011	T=1.86, p=.096	T=3.59, p=.004	T=3.11, p=.011
O2	T=1.78, p=.101	T=1.54, p=.159	T=3.56, p=.004	T=5.40, p=.000

All values are expressed as Student's T and its respective *p* value. Non-significant paired t-tests with ps>0.2 are printed in bold typeface.

Abbreviations: see Table 1.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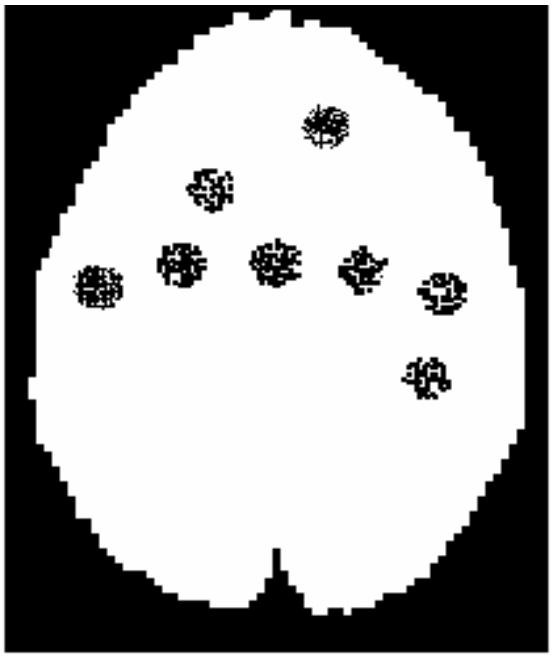

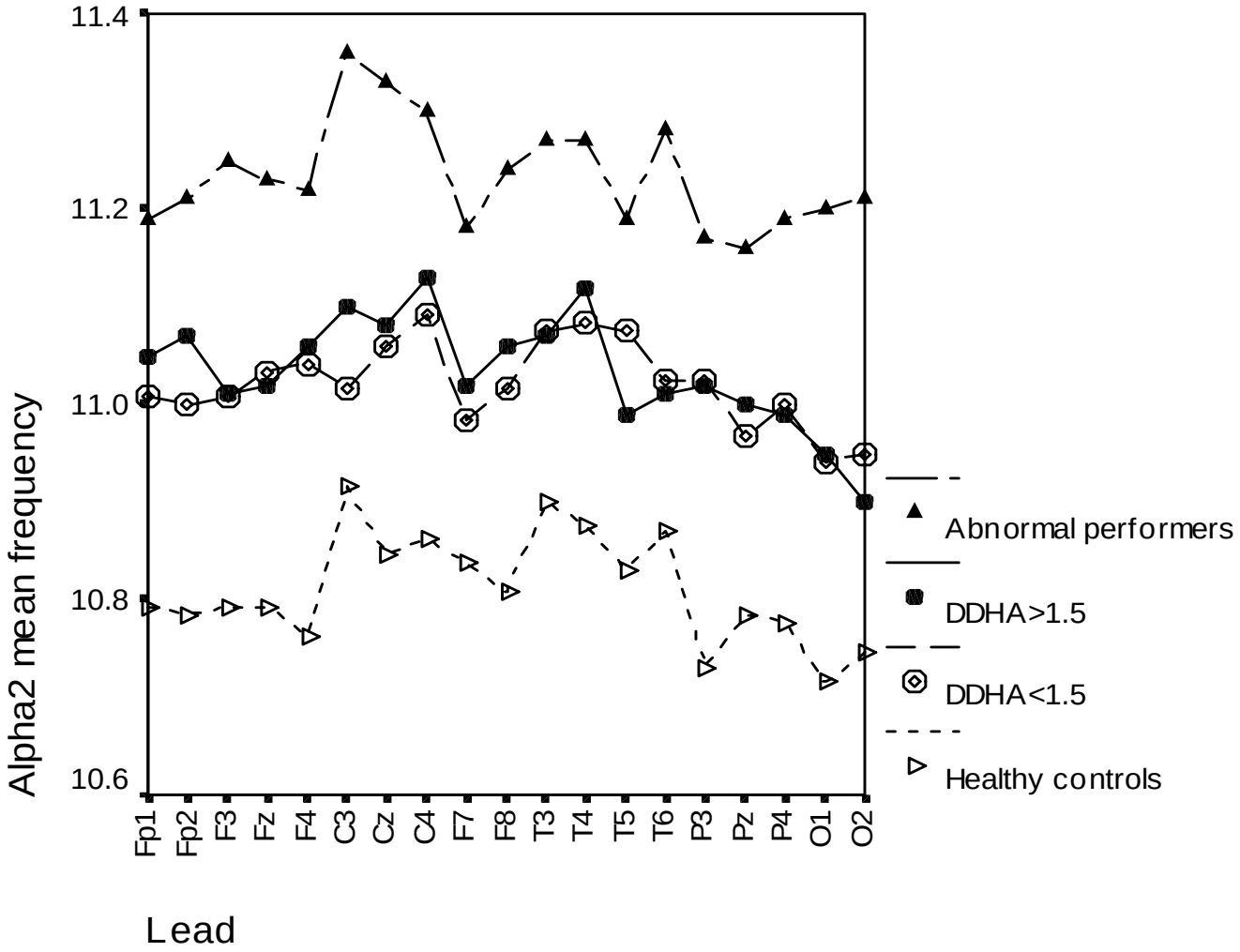
11.4
11.2
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10.8
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Alpha2 mean frequency
Fp1
Fp2
F3
Fz
F4
C3
Cz
C4
F7
F8
T3
T4
T5
T6
P3
Pz
P4
O1
O2
Lead
Abnormal performers
DDHA>1.5
DDHA<1.5
Healthy controls

Fig. 1. An example of the 5 move problems of the Tower of London Test. The start state of a problem is shown on the left and the goal state is shown on the right. Patients were informed about minimum number of moves at the start of each task.

Fig. 2. Derivations (dotted areas) in which the relationships between the performance on the Tower of London Test and alpha2 mean frequencies were significant (Adjusted R^2s = .098 - .173, Fs(2) = 3.45-5.72, ps = .041-.006, powers = 0.62-0.84).

Fig. 3. Distribution of alpha2 mean frequencies at 19 leads in healthy controls (n=12), heroin abusers who performed TLT abnormally (n=10), heroin abusers of DDHA<1.5 and DDHA>1.5 years who performed TLT in normal range (n=12 and n=11, respectively).